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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,099	01/05/2000	ANTHONY P. ADAMIS	50069/002002	1198

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EXAMINER	
BAKER, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/478,099	Applicant(s) ADAMIS ET AL.	
	Examiner Anne Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☒ Interview Summary (PTO-413) Paper No(s). *13* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

File

DETAILED ACTION

The response filed May 29, 2001 (Paper No. 9) has been entered. The response filed February 26, 2002 (Paper No. 12) has been entered. Applicants' election, without traverse, of Group II, Claims 1-18 in Paper No. 9 is acknowledged. The elected invention is directed to a method for the delivery of a therapeutic or diagnostic agent to the eye of a mammal, wherein the agent is a nucleic acid.

Claims 1-20 remain pending in the instant application.

Claims 19 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Claims 1-18 embrace multiple inventions, and are examined herein only to the extent that they encompass the elected subject matter.

Claims 1-18 are examined herein.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the mailing or post office address of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

The Post Office address of each inventor is incomplete.

The Residence address of each inventor is incomplete.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action mailed 8/15/01 (Paper No. 10) and reiterated here, and for the reasons set forth herein below, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure for the claimed methods because the specification teaches that the only use for the methods is for gene therapy, but the specification does not enable this use. The specification does not teach how to use the claimed methods in gene therapy applications, for the following reasons.

The specification teaches that a desired polypeptide can be expressed from a recombinant nucleic acid encoding the desired polypeptide (p. 8, lines 18-19). The specification further teaches that the nucleic acids are genes and that they encode polypeptides (p. 9, lines 5-15). At page 13, the specification teaches that the nucleic acid molecules delivered to the eye include vectors for gene transfer, such as DNA plasmids, or viral vectors (p. 13, lines 8-10). Thus, the claims are clearly directed to methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification fails to teach any method for transferring a therapeutic or diagnostic nucleic acid and/or gene into a target cell of the eye and expressing that gene at a level sufficient to produce a therapeutic effect in a diseased immunocompetent animal. The specification does not provide any guidance as to the level of gene

expression required, the type of gene transfer vector to be used, the particular therapeutic nucleic acid molecule/gene to be used, the number of transduced cells needed, the route and time course of administration, when, where, or for how long the therapeutic gene should be expressed, the frequency of administration of the gene therapy vector, or in some embodiments, the intended target tissue, for treatment of any pathological condition in an immunocompetent animal. The specification also lacks any working examples showing that the contemplated therapeutic nucleic acid vector, once delivered to the appropriate site, would be expressed at a level sufficient to provide adequate product to effect the desired therapy in an immunocompetent animal. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods for *in vivo* gene therapy. Thus, absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect in an immunocompetent animal, such as a human, the claims directed to gene therapy are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for used of the claimed methods for the treatment of any disease because the specification does not offer specific guidance for treating any eye disease in an immunocompetent animal. As gene therapy is not routine for the reasons discussed above, undue experimentation would have been required for one skilled in the art to treat any eye disease using the claimed method.

The specification fails to provide an enabling disclosure for targeting appropriate cells for the treatment of the diseases referred to in the specification. The specification contemplates treating a wide variety of retinal and choroidal diseases, including macular degeneration, diabetic retinopathy, retinitis pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal ischemia, proliferative vitreoretinopathy, and retinopathy of prematurity. Only general guidance is offered with regard to targeting strategies known in the art. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. More importantly, the disclosure does not offer a solution to this problem. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that "for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain et al. Review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under

Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Even expression studies in animals are often not predictive that the same or similar results can be achieved in patients or that such expression would alleviate clinical symptoms. For example, although researchers have demonstrated expression of the CFTR gene in the surface airway cells of laboratory animals, problems transferring sufficient quantities of the CFTR gene into patients' cells have prevented the method from providing therapeutic benefit. Furthermore, the viral vector used to transfer the gene provoked an immune reaction in some patients (Marshall, 1995, p. 1052). Marshall emphasizes that the central challenge in the field of gene therapy is to find safe vectors capable of transporting genes efficiently into target cells, and getting the cells to express the genes once they are inserted. These problems remain unresolved. Thus, the claims directed to *in vivo* gene therapy are not enabled because the specification fails to disclose a method for transferring an unspecified therapeutic gene into the appropriate cells of the eye and expressing that unspecified gene at a therapeutic level.

The specification fails to provide an enabling disclosure for the claimed nucleic acid delivery method because the specification only teaches how to deliver agents across the sclera using an osmotic pump, but does not teach how to use any other device to deliver agents across the sclera, nor does it teach how to deliver agents across the sclera in the absence of an osmotic pump. Claims 1 and 8-18 recite a "means for facilitating the transport of said agent through the sclera." Although the specification

contemplates that other devices or means, such as mechanical or solid state devices, microchips, or polymers, could be used to deliver various agents across the sclera, the working examples are exclusively directed to the use of an osmotic pump to facilitate transport of the agent through the sclera, and the specification does not provide specific guidance with regard to the use of any other "means for facilitating the transport of said agent through the sclera," as recited in Claims 1 and 11. It is noted that Claims 2-10 and 12-18, do not require use of a "means for facilitating the transport of said agent through the sclera." However, the specification teaches that an osmotic pump is required to facilitate transport of the agent through the sclera and therefore is an essential element of the invention. There are no specific teachings for practicing the claimed invention in the absence of an osmotic pump.

The specification fails to provide an enabling disclosure for delivering agents larger than 150 kDa. The working examples of the specification are directed to the delivery of immunoglobulins through the sclera, with the aid of an osmotic pump. However, the specification does not teach how to deliver agents larger than 150 kDa. At page 20 of the specification, in Table 1, the disclosure teaches that sclera is somewhat permeable to an agent having a molecular weight of 150 kDa. However, the permeability is much lower than that of smaller molecules, and there is no specific guidance for the use of agents larger than 150 kDa.

In view of the quantity of experimentation necessary to determine appropriate parameters for the claimed method for treatment of a pathological condition in immunocompetent animals, and given the lack of applicable working examples demonstrating an *in vivo* effect in an immunocompetent animal, the limited guidance in the specification, particularly with regard to the nucleic acid that is to be delivered, the broad scope of the claims, the lack of a working example for *in vivo* gene therapy, and the unpredictability for using the claimed methods in any gene therapy application to produce the desired therapeutic effect, undue experimentation would have been required for one skilled in the art to practice the claimed invention.

At page 1 of the response, Applicants argue that the Examiner has not questioned whether the specification adequately enables the delivery of a nucleic acid molecule into the eye across the sclera. However, this is incorrect. Applicants attention is particularly directed to the discussion of targeted gene delivery at pages 4-5 of the Office Action of Paper No. 10 (mailed 8/15/01). The rejection specifically discusses the failure of the specification to enable delivery of the nucleic acid to the desired location, particularly in adequate amounts. Applicants further argue that the only question is whether, once delivered, the nucleic acid would be therapeutically effective. Applicants refer to a publication said to be attached to the response as Exhibit A. However, the Examiner did not receive Exhibit A and no citation is provided for the publication. The Examiner left a message for Paul Clark requesting the reference, but did not hear back. See the Interview Summary of May 14, 2002. The Examiner cannot comment on evidence not of record. However, it is noted that Applicants refer to an anti-VEGF nucleic acid molecule. The Examiner does not find a description of an anti-VEGF nucleic molecule in the specification as-filed. Applicants have not pointed to support in the specification for use of an anti-VEGF nucleic acid molecule.

At page 3 of the response, Applicants argue that nucleic acid molecules do not need to enter cells and no transfection need occur for a therapeutic benefit to be realized. Without commenting on the asserted therapeutic benefit to which Applicants refer as being taught in the missing publication, it is noted that the specification clearly contemplates using the nucleic acid agents for gene transfer (p. 13, lines 8-10) and moreover, the claims clearly encompass gene therapy approaches to treating the various diseases recited in the claims.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The nucleic acid molecule is an essential element of the claimed invention. However, the specification does not describe any nucleic acid molecule that could be used in practicing the method of the invention, for diagnostic or therapeutic purposes. At the outset it is noted that Table 1 of the specification discloses the permeability coefficient of the sclera for agents of various sizes. At 150 kDa and 8.25 nm molecular radius, the permeability coefficient is much lower than that of smaller molecules tested. Given that the specification does not provide specific guidance for using the method of the invention to deliver molecules larger than 150 kDa, the size of the nucleic acid being delivered could not be larger than 230 base pairs (using an average molecular weight of 660 Da/base pair). However, the specification does not describe any diagnostic or therapeutic nucleic acid molecules that could be delivered across the sclera by the method of the invention. Furthermore, the specification does not describe nucleic acids that could be used to treat a retinal or choroidal disease, using the claimed delivery method. The specification does not describe a nucleic acid that could be used to treat macular degeneration, diabetic retinopathy, retinitis pigmentosa and other retinal degenerations, retinal vein occlusions, sickle cell retinopathy, glaucoma, choroidal neovascularization, retinal neovascularization, retinal edema, retinal ischemia, proliferative vitreoretinopathy, or retinopathy of prematurity, as claimed. In the absence of a written description of the nucleic acid agent, the claimed method lacks written description because the nucleic acid agent is an essential element of the claimed method. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, no nucleic acid molecules that can be used therapeutically or diagnostically and delivered by the method of the invention are described. Next then, it is determined whether a representative number of species have been

sufficiently described by other relevant identifying characteristics. In this case, no particular identifying characteristics are described. There is insufficient guidance regarding which nucleic acid agents will be successfully delivered across the sclera and function *in vivo* in the manner intended. Thus, the specification does not describe any nucleic acid molecule that can be used in the claimed method. This limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of nucleic acid agents for diagnostic and therapeutic uses in the eye. Thus, it is concluded that the written description requirement is not satisfied for methods of using the genus of nucleic acids recited in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18 are indefinite because they encompass non-elected subject matter. The claims cover delivery of polypeptides and organic molecules, but the elected invention is limited to delivery of nucleic acids. Thus, the metes and bounds of the claims are not clearly set forth.

Claims 1-18 are indefinite in their recitation of "targeted" because the specification, at page 7, defines "targeted" to mean that the agent is delivered only to the sclera, but the claims recited "targeted" delivery "to the eye." Thus, it is unclear how the term "targeted" should be interpreted in the context of the present claim language.

Claims 12-14 are indefinite in their recitation of "said device" because the term lacks antecedent basis. Claims 1, 2, and 5 do not recite a "device."

Claims 2-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP

§ 2172.01. The omitted elements are: a pump for facilitating transport of the nucleic acid through the sclera. The specification teaches that a pump is required to achieve targeted unidirectional delivery of the nucleic acid to the eye.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER